University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2016

Bleeding Risk Profile in Patients With Symptomatic Peripheral Artery Disease

Baumann, Frederic ; Husmann, Marc ; Benenati, James F ; Katzen, Barry T ; Del Conde, Ian

Abstract: PURPOSE To assess the bleeding risk profile using the HAS-BLED score in patients with symptomatic peripheral artery disease (PAD). METHODS A post hoc analysis was performed using data from a series of 115 consecutive patients (mean age 72.4±11.4 years; 68 men) with symptomatic PAD undergoing endovascular revascularization. The endpoint of the study was to assess bleeding risk using the 9-point HAS-BLED score, which was previously validated in cohorts of patients with and without atrial fibrillation. For the purpose of this study, the low (0-1), intermediate (2), and high-risk (3) scores were stratified as low/intermediate risk (HAS-BLED <3) vs high risk (HAS-BLED 3). RESULTS The mean HAS-BLED score was 2.76±1.16; 64 (56%) patients had a HAS-BLED score 3.0. Patients with PAD Rutherford category 5/6 ischemia had an even higher mean HAS-BLED score (3.20±1.12). Logistic regression analysis revealed aortoiliac or femoropopliteal segment involvement, chronic kidney disease, as well as Rutherford category 5/6, to be independent risk factors associated with a HAS-BLED score 3. CONCLUSION Patients with PAD, especially those presenting with Rutherford category 5/6 ischemic symptoms, have high HAS-BLED scores, suggesting increased risk for major bleeding. Prospective clinical validation of the HAS-BLED score in patients with PAD may help with the risk-benefit assessment when prescribing antithrombotic therapy.

DOI: https://doi.org/10.1177/1526602816637621

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-123417
Journal Article
Published Version

Originally published at:
Baumann, Frederic; Husmann, Marc; Benenati, James F; Katzen, Barry T; Del Conde, Ian (2016). Bleeding Risk Profile in Patients With Symptomatic Peripheral Artery Disease. Journal of Endovascular Therapy, 23(3):468-471.
DOI: https://doi.org/10.1177/1526602816637621

Page Proof Instructions and Queries

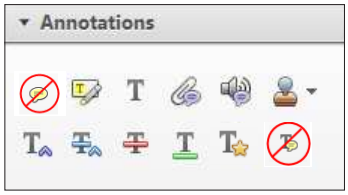
Journal title: Journal of Endovascular Therapy

Article Number: 637621

Greetings, and thank you for publishing with SAGE. We have prepared this page proof for your review. Please respond to each of the below queries by digitally marking this PDF using Adobe Reader.

Click "Comment" in the upper right corner of Adobe Reader to access the mark-up tools as follows:

For textual edits, please use the "Annotations" tools. Please refrain from using the two tools crossed out below, as data loss can occur when using these tools.



For formatting requests, questions, or other complicated changes, please insert a comment using "Drawing Markups."

Detailed annotation guidelines can be viewed at: http://www.sagepub.com/repository/binaries/pdfs/AnnotationGuidelines.pdf

Adobe Reader can be downloaded (free) at: http://www.adobe.com/products/reader.html.

No.	Query
	Please confirm that all author information, including names, affiliations, sequence, and contact details, is correct.
	Please review the entire document for typographical errors, mathematical errors, and any other necessary corrections; check headings, tables, and figures.
	Please confirm you have reviewed this proof to your satisfaction and understand this is your final opportunity for review prior to publication.
	Please confirm that the Funding and Conflict of Interest statements are accurate.

Clinical Investigation

JOURNAL OF ENDOVASCULAR THERAPY
An official publication of the International Society of Endovascular Specialists
A SAGE Publication

Journal of Endovascular Therapy
1–4
© The Author(s) 2016
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1526602816637621
www.jevt.org
SAGE

Bleeding Risk Profile in Patients With Symptomatic Peripheral Artery Disease

Frederic Baumann, MD[1], Marc Husmann, MD[2], James F. Benenati, MD[1], Barry T. Katzen, MD[1], and Ian Del Conde, MD[1]

Abstract

Purpose: To assess the bleeding risk profile using the HAS-BLED score in patients with symptomatic peripheral artery disease (PAD) as a background for intensifying antithrombotic therapy to prevent major adverse cardiovascular and limb events. **Methods:** A post hoc analysis was performed using data from a series of 115 consecutive patients (mean age 72.4±11.4 years; 68 men) with symptomatic PAD undergoing endovascular revascularization. The endpoint of the study was to assess bleeding risk using the 9-point HAS-BLED score, which was previously validated in cohorts of patients with and without atrial fibrillation. For the purpose of this study, the original low (0–1), intermediate (2), and high-risk (≥3) scores were stratified as low/intermediate risk (HAS-BLED <3) vs high risk (HAS-BLED ≥3). **Results:** The mean HAS-BLED score was 2.76±1.16; 51 (56%) patients had a HAS-BLED score ≥3.0. Patients with PAD Rutherford category 5/6 ischemia had an even higher mean HAS-BLED score (3.20±1.12). Logistic regression analysis revealed aortoiliac or femoropopliteal segment involvement, chronic kidney disease, as well as Rutherford category 5/6, to be independent risk factors associated with a HAS-BLED score ≥3. **Conclusion:** Patients with PAD, especially those presenting with Rutherford category 5/6 ischemic symptoms, have high HAS-BLED scores, suggesting increased risk for major bleeding. Prospective clinical validation of the HAS-BLED score in patients with PAD may help with the risk-benefit assessment when prescribing antithrombotic therapy.

Keywords

antithrombotic therapy, bleeding, femoropopliteal segment, HAS-BLED score, aortoiliac segment, peripheral artery disease

Introduction

Patients with peripheral artery disease (PAD) are at high risk for cardiovascular as well as major adverse limb events, including acute limb ischemia, need for revascularization, and amputation.[1–3] There has been increasing interest in intensifying antithrombotic therapy in patients with PAD to reduce these adverse cardiovascular and limb events. Use of new classes of antiplatelet agents, such as vorapaxar (a protease-activated receptor–1 inhibitor) and third-generation thienopyridines, prolonged dual antiplatelet therapy, and even the combination of anticoagulation with antiplatelet therapy are being actively investigated in patients with PAD. However, PAD patients, especially those with critical limb ischemia (CLI), constitute a frail population with various comorbidities that may increase the risk of major bleeding.[4] The risks and benefits of enhanced antithrombotic therapy must therefore be carefully weighed.

To our knowledge, there are no bleeding risk scores that have been prospectively validated in patients with PAD. However, several independent bleeding risk factors have been identified, prospectively validated, and incorporated into clinical bleeding risk scores that are used in clinical practice for patients with and without baseline atrial fibrillation (AF).[5] One of the best validated scores is HAS-BLED [*h*ypertension, *a*bnormal renal or liver function, *s*troke, history of or predisposition to *b*leeding, *l*abile INR, *e*lderly age (>65 years), and *d*rugs or alcohol].[6] Lip et al[7] recently reported that the predictive value of an elevated HAS-BLED score also applied to individuals from a community cohort *without* baseline AF.

The purpose of the present study was to evaluate the bleeding risk profile in an all-comers series of PAD patients and to analyze differences in HAS-BLED profiles among

[1]Miami Cardiac & Vascular Institute, Baptist Hospital of Miami, FL, USA
[2]Clinic for Angiology, University Hospital of Zurich and University of Zurich, Switzerland

Corresponding Author:
Ian Del Conde, Baptist Hospital of Miami, Miami Cardiac & Vascular Institute, 8900 North Kendall Drive, Miami, FL 33176 USA.
Email: iand@baptisthealth.net

different PAD subgroups stratified by severity of ischemia based on the Rutherford classification.

Methods

Study Design

A post hoc analysis was performed assessing the bleeding risk in consecutive patients with symptomatic PAD referred to a tertiary vascular center for endovascular revascularization between 2014 and 2015. Data collection was performed prospectively for performance improvement purposes. Approval from the institutional review board was obtained to analyze and publish the data. This study was performed in accordance with the Declaration of Helsinki[8] and the Health Insurance Portability and Accountability Act.

Bleeding Risk Assessment

The 9 variables included in the HAS-BLED score, each scored as 1 point, were uncontrolled hypertension (systolic blood pressure >160 mm Hg), abnormal liver function (aspartate aminotransferase or alanine aminotransferase >3× upper limit), abnormal renal function (serum creatinine ≥2.0 mg/dL), previous stroke, history of bleeding or anemia, labile international normalized ratio (INR) (if on vitamin K antagonist), age >65 years, drugs (antiplatelet therapy, nonsteroidal anti-inflammatory therapy), and alcohol (≥8 standard drinks).[6,9] In the original HAS-BLED scheme for estimating bleeding risks in patients with AF treated with anticoagulation, a HAS-BLED score of 0–1 was considered low risk, a score of 2 was intermediate risk, and a score ≥3 was considered high risk for major bleeding.[10] For the purpose of this study, the score was stratified only for low/intermediate risk (HAS-BLED <3) vs high risk (HAS-BLED ≥3).

Definitions

In this study, anemia was defined as a hematocrit ≤32%. A labile INR was defined as <60% of the time in the therapeutic range. The assessment of PAD was predicated on the PARC (Peripheral Academic Research Consortium) definitions,[11] using the Rutherford classification to describe the severity of PAD (0=asymptomatic, 1=mild claudication, 2=moderate claudication, 3=severe claudication, 4=rest pain, 5=ischemic ulceration, 6=ischemic gangrene). In addition, lesions treated were categorized as aortoiliac, femoropopliteal, infrapopliteal, or multisegment if affecting >1 of these segments.

Patient Population

Between 2014 and 2015, 115 consecutive patients (mean age 72.4±11.4 years; 68 men) with symptomatic PAD underwent endovascular revascularization at our center.

Table 1. Baseline Demographics and Bleeding Risk Factors of the 115-Patient Group.[a]

Women	47 (40.9)
Age, y	72.4±11.4
GFR, mL/min/1.73 m^2	63.7±39.1
Hypertension	107 (93.0)
Uncontrolled	57 (49.6)
Diabetes mellitus	56 (48.7)
Insulin-dependent	28 (24.3)
Liver dysfunction	3 (2.6)
Active tobacco	25 (21.7)
Former tobacco	43 (37.4.)
Alcohol	4 (3.5)
Drugs	2 (1.7)
Coronary artery disease	48 (41.7)
Congestive heart failure	17 (14.8)
Transient ischemic attack	7 (6.1)
Stroke	16 (13.9)
CKD stage	
1 (GFR >90)	20 (17.4)
2 (GFR >60 to <90)	30 (26.1)
3 (GFR >30 to <60)	38 (33.0)
4 (GFR >15 to <30)	14 (12.2)
5 (GFR <15 or dialysis)	13 (11.3)
Peripheral artery disease	69 (60.0)
Bleeding history or predisposition	28 (24.3)
Low platelet count	5 (4.3)
Rutherford category	
1	0 (0.0)
2	14 (12.2)
3	33 (28.7)
4	23 (20.0)
5	39 (33.9)
6	6 (5.2)

Abbreviations: CKD, chronic kidney disease based on glomerular filtration rate (GFR) calculated by Cockcroft-Gault formula.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage).

Table 1 provides detailed information on the baseline demographics and risk factors of these patients, and Table 2 lists the arterial segments involved and whether patients had prior revascularization.

Statistical Analysis

Categorical variables are presented as numbers (percentages) and were compared using a chi-square test; continuous variables were reported as means ± standard deviation. A homogenous distribution was assessed using an independent *t* test or the Kolmogorov-Smirnov test. Independent variables associated with a high risk for bleeding (HAS-BLED ≥3) were identified by logistic regression analysis; the results are presented as the odds ratio (OR) and 95%

Table 2. Level of Disease, Prior Revascularization, Amputation, and HAS-BLED Scores in the 115 Study Patients.[a]

Level of disease	
Aortoiliac	36 (31.3)
Femoropopliteal	88 (76.5)
Infrapopliteal	51 (44.3)
Multisegment	56 (48.7)
Prior amputation	
Minor (below ankle)	14 (12.2)
Major	6 (5.2)
Prior revascularization	
Endovascular	48 (41.7)
Surgical	20 (17.4)
HAS-BLED score	
0	0 (0.0)
1	16 (13.9)
2	35 (30.4)
3	34 (29.6)
4	23 (20.0)
5	5 (4.4)
6	2 (1.7)

Abbreviations: HAS-BLED, *h*ypertension, *a*bnormal renal or liver function, stroke, history of or predisposition to *b*leeding, *l*abile INR, elderly age (>65 years), and *d*rugs or alcohol.
[a]Data are given as the counts (percentage).

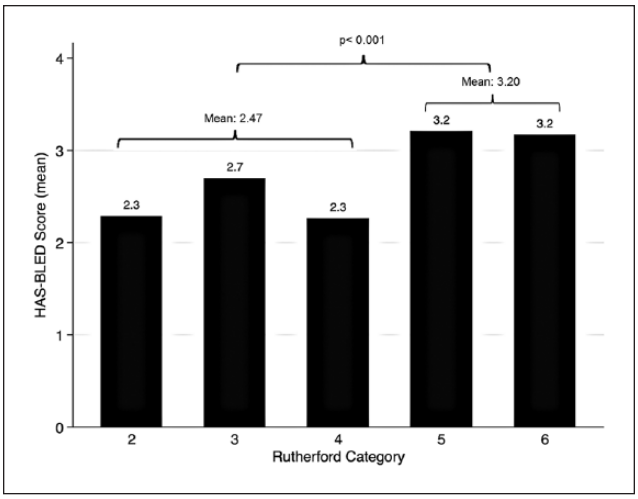


Figure 1. Mean HAS-BLED scores according to Rutherford category. HAS-BLED, *h*ypertension, *a*bnormal renal or liver function, stroke, history of or predisposition to *b*leeding, *l*abile INR, elderly age (>65 years), and *d*rugs or alcohol.

confidence interval (CI). A $p<0.05$ was considered to indicate statistical significance. Statistical analysis was performed using STATA software (version 14.0; StataCorp, College Station, TX, USA).

Results

The overall mean HAS-BLED score across the 115 patients was 2.76±1.16. There were no patients with a HAS-BLED score of 0; 51 (55.7%) patients had a HAS-BLED score ≥3 (Table 2). Stratifying the mean HAS-BLED scores according to Rutherford categories (RC), patients with tissue loss (ie, RC 5/6) had a significantly higher HAS-BLED score compared to patients with RC 2–4 symptoms (3.20±1.12 vs 2.47±1.10, $p<0.001$; Figure 1). The mean HAS-BLED score in patients with RC 4 ischemia was more similar to patients with RC 2–3 symptoms and significantly lower compared to patients with RC 5/6 ischemia ($p<0.001$, Figure 1). Similarly, a HAS-BLED score ≥3 was more common in patients with RC 5/6 than in patients with RC 2–4 (73.3% vs 44.3%, $p=0.002$). The main clinical variables represented in HAS-BLED that drove these differences included advanced renal insufficiency (creatinine >2.0 mg/dL) and a history of bleeding or predisposition to bleeding ($p\leq0.004$ for both).

Logistic regression analysis revealed that involvement of the femoropopliteal (OR 3.17, 95% CI 1.03 to 9.75, $p=0.04$) or aortoiliac segments (OR 3.15, 95% CI 1.05 to 9.41, $p=0.04$), RC 5/6 ischemia (OR 3.52, 95% CI 1.39 to 8.95, $p=0.008$), and chronic kidney disease stage ≥2 defined by a glomerular filtration rate <60 mL/min/1.73 m^2 (OR 3.37, 95% CI 1.42 to 8.00, $p=0.006$) were independent risk factors for a HAS-BLED score ≥3.

Discussion

The current study shows that patients with symptomatic PAD had an elevated HAS-BLED score, which was even higher in the setting of ischemic tissue loss. Almost three quarters of patients with RC 5/6 ischemia had a HAS-BLED score ≥3, suggesting that this PAD subgroup is at increased risk of major bleeding compared to patients with RC 2–4 symptoms.

This was a qualitative rather than quantitative study. We did not have long-term follow-up data for patients and could not capture actual bleeding events. The absolute risk of major bleeding events therefore cannot be derived from our data. However, to put the HAS-BLED scores into perspective, one may consider the performance of HAS-BLED in other patient populations. In a cohort of "real world" patients with AF receiving anticoagulation, a HAS-BLED score ≥3.0 carried a 3-fold increase in the rate of major bleeding (defined as hospitalization or death from major bleeding) compared to patients with a HAS-BLED score of 0 or 1 (8.1 vs 2.6 events per 100 person-years, respectively).[10] The predictive value of HAS-BLED also applies in patients *without* baseline AF.[7] In the Chin-Shan Community Cohort study,[7] the risk for intracranial hemorrhage rose with increasing HAS-BLED scores, with a C-statistic of 0.72. In that cohort study, 40% of individuals had a HAS-BLED score of 0, and 4.3% had a HAS-BLED

score ≥3.0. The rate of intracranial hemorrhages increased with higher HAS-BLED scores: 0.2 events per 1000 patient-years for a HAS-BLED score of 0 and 4.1 intracranial bleeds per 1000 patient-years for a HAS-BLED score ≥3. In our study, no patients with PAD had a HAS-BLED score of 0, and more than half had a HAS-BLED score ≥3.0. We interpret these findings as an indication that patients with symptomatic PAD, especially those with ischemic ulceration or gangrene, are at increased risk of major bleeding, including intracranial hemorrhage.

To further understand the significance of the elevated HAS-BLED among patients with PAD, we determined the HAS-BLED score in a cohort of age- and gender-matched patients (n=39) *without* PAD. These patients did not have a prior diagnosis of PAD, had no lower extremity symptoms on exertion, and had normal bilateral pedal pulses on physical examination. The proportion of non-PAD patients who had a HAS-BLED score >3 was 5.1% (2/39) compared with 26.1% (30/115) in the PAD cohort (p=0.005).

An interesting finding in our study is that HAS-BLED scores were significantly higher in patients with Rutherford category 5/6 ischemia compared with RC 2–4 patients. One could have anticipated that patients with RC 4 (ischemic rest pain) would have had a similar HAS-BLED profile compared to patients with RC 5/6 symptoms, as all of these patients are grouped into the standard definition of CLI. However, we found that RC 4 patients had a mean HAS-BLED score similar to patients with intermittent claudication (RC 2/3). We hypothesize that RC 4 patients are biologically more similar to patients with intermittent claudication (RC 2/3) and that they "shift" to an advanced stage with CLI due to an acute-on-chronic event. In contrast, RC 5/6 may represent more of a chronic status with CLI.

Conclusion

Patients with symptomatic PAD have elevated HAS-BLED scores compared with the general population. Even among PAD patients, those with ischemic ulceration or gangrene (ie, RC 5/6) have higher HAS-BLED scores compared to the other PAD subgroups. These observations suggest that PAD patients are at increased risk of bleeding complications. The application of HAS-BLED or similar bleeding risk scores warrant further scrutiny, including prospective validation for use in PAD patients and would provide a great clinical tool to assess the risk-benefit ratio of antithrombotic therapy in PAD patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. European Stroke Organisation. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2851-2906.
2. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340.
3. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.
4. Diehm N, Shang A, Silvestro A, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. *Eur J Vasc Endovasc Surg*. 2006;31:59–63.
5. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Thromb Haemost*. 2011;106:997–1011.
6. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.
7. Lip GY, Lin HJ, Hsu HC, et al. Comparative assessment of the HAS-BLED score with other published bleeding risk scoring schemes, for intracranial haemorrhage risk in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. *Int J Cardiol*. 2013;168:1832–1836.
8. World Medical Association General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Int Bioethique*. 2004;15:124–129.
9. Dzeshka MS, Lane DA, Lip GY. Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS2, CHA2 DS2 -VASc, R2 CHADS2, HAS-BLED, ATRIA, and more). *Clin Cardiol*. 2014;37:634–644.
10. Olesen JB, Lip GY, Hansen PR, et al. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb Haemost*. 2011;9:1460–1467.
11. Patel MR, Conte MS, Cutlip DE, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). *J Am Coll Cardiol*. 2015;65:931–941.